REMARKS

Status of the Claims

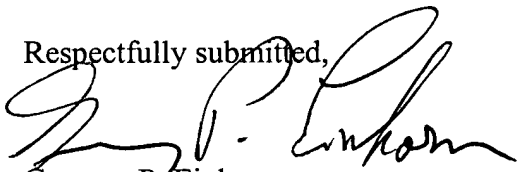
Upon entry of Applicants' amendment dated June 11, 1999, claims 10 to 14 and 18 to 51 are pending in the present application (claims 31 to 51 were newly added in the 6/11/99 amendment). Claims 1 to 9 and 15 to 17 were withdrawn from further consideration as being drawn to a non-elected species. New claims 52 and 53 are added and claims 11 and 30 are canceled in the instant response. Thus, *after* entry of the instant amendment, claims 10, 12 to 14, 18 to 29 and 31 to 53 will be pending. For the Examiner's convenience, the pending claims *after* entry of the instant amendment is attached as Appendix A.

The Communication Dated August 27, 1999

Applicants thank the Examiner for noting the inadvertent errors in the amendment to claims 11 and 30 in Applicants' response dated June 11, 1999. The Examiner invited Applicants to cancel claims 11 and 30 and provide new claims to provide clarity. In response, Applicants have canceled claims 11 and 30 and added new claims 52 and 53 to address the Examiner's concerns.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned or Bill Smith at 415-576-0200.

Respectfully submitted,



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APPENDIX A

Pending Claims *After* Entry Amendment Submitted Sept, 1999

USSN 08/728,463, filed October 10, 1996
for: TRANSGENIC NON-HUMAN ANIMALS
CAPABLE OF PRODUCING HETEROLOGOUS ANTIBODIES
Inventors: Lonberg et al.
TTC No. 014643-009020US

10. (Amended) A transformed cell comprising a nucleic acid encoding at least a portion of a human sequence immunoglobulin polypeptide,

wherein the human sequence immunoglobulin polypeptide specifically binds a human antigen,

wherein the cell produces a detectable amount of the immunoglobulin.

N.E. [11. canceled]

12. (Amended) The transformed cell of claim 10, wherein the human sequence immunoglobulin binds human CD4 or an antigenic fragment thereof.

13. (Amended) A human sequence immunoglobulin that specifically binds human CD4 or antigenic fragment thereof, wherein said immunoglobulin comprises a human sequence light chain or human sequence heavy chain variable region having similar affinity to a human CD4, or antigenic fragment thereof, as a human sequence immunoglobulin comprising a variable region comprising an amino acid sequence encoded by a nucleic acid with a sequence as set forth in SEQ ID NO:1, . SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10.

14. (Amended) The human sequence immunoglobulin of claim 13 wherein the immunoglobulin comprises an amino acid sequence as set forth in SEQ ID NO:61 or SEQ ID NO:62.

18. A human anti-CD4 immunoglobulin that specifically binds CD4 from humans and specifically binds CD4 from at least one non-human primate.

19. The immunoglobulin of claim 18 wherein the non-human primate is Rhesus monkey, cynomolgus monkey, or chimpanzee.

20. The immunoglobulin of claim 19 wherein the human anti-CD4 immunoglobulin specifically binds CD4 from both rhesus monkey and cynomolgus monkey.

21. The immunoglobulin of claim 19 wherein the human anti-CD4 immunoglobulin specifically binds CD4 from rhesus monkey, cynomolgus monkey and chimpanzee.

22. (Amended) A human sequence immunoglobulin comprising a VH4-34 segment, a DXP'1 segment, a JH4 segment, and a heavy chain CDR3 region comprising the sequence DITMVRGPH (SEQ ID NO:63).

23. (Amended) A human sequence immunoglobulin comprising a VH5-51 segment, a DHQ52 segment, a JH2 segment, and a heavy chain CDR3 region comprising the sequence PANWNWYFVL (SEQ ID NO:64).

24. (Amended) A human sequence immunoglobulin comprising a VH4-34 segment, a JH5 segment, and a heavy chain CDR3 region comprising the sequence VINWFDP (SEQ ID NO:65).

25. (Amended) A human sequence immunoglobulin comprising a VH5-51 segment, a DHQ52 segment, a JH4 segment , and a heavy chain CDR3 region comprising the sequence DQLGLFDY (SEQ ID NO:66).

26. (Amended) A human sequence immunoglobulin comprising a VkA27/A11 segment, a Jk4 segment, and a light chain CDR3 region comprising the sequence QQYGSSPLT (SEQ ID NO:67).

27. (Amended) A human sequence immunoglobulin comprising a VkL18 segment, a Jk4 segment, and a light chain CDR3 region comprising the sequence QQFISYPQLT (SEQ ID NO:68).

28. (Amended) A human sequence immunoglobulin comprising a VkL19 segment, a Jk2 segment, and a light chain CDR3 region comprising the sequence QQANSFPYT (SEQ ID NO:69).

29. (Amended) A human sequence immunoglobulin comprising a VkL15 segment, a Jk2 segment, and a light chain CDR3 region comprising the sequence QQYDSYPYT (SEQ ID NO:70).

[30. canceled]

31. (added in amendment 6/11/99) An isolated human sequence immunoglobulin which binds to human CD4 or antigenic fragment thereof with a K_a affinity of at least about 10^8 M^{-1}.

32. (added in amendment 6/11/99) The isolated human sequence immunoglobulin of claim 31, where the K_a affinity is at least about 10^9 M^{-1}.

33. (added in amendment 6/11/99) The isolated human sequence immunoglobulin of claim 31, where the immunoglobulin is a human sequence monoclonal antibody.

34. (added in amendment 6/11/99) The isolated human sequence immunoglobulin of claim 33, where the human sequence monoclonal antibody is produced by a hybridoma made by fusing an immortal cell with a lymphocyte isolated from a transgenic mouse.

35. (added in amendment 6/11/99) The isolated human sequence immunoglobulin of claim 34, where the hybridoma is selected from the group consisting of 1E11.15, 6C1.10, 1G1.9, 6G5.1, 10C5.6, 2E4.2, 4D1.4, 7G2.2 1F8.2 and 1G2.10.

36. (added in amendment 6/11/99) The isolated human sequence immunoglobulin of claim 31, where the immunoglobulin is expressed from a nucleic acid sequence initially isolated from a lymphocyte from a transgenic mouse.

37. (added in amendment 6/11/99) An isolated human sequence immunoglobulin that specifically binds human CD4 or antigenic fragment thereof comprising a human sequence immunoglobulin light chain polypeptide having a VJ junction comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, and SEQ ID NO:10.

38. (added in amendment 6/11/99) The isolated human sequence immunoglobulin of claim 35, wherein the immunoglobulin binds to a human CD4 or antigenic fragment thereof with a K_a affinity of at least about 10^8 M^{-1}.

39. (added in amendment 6/11/99) The isolated human sequence immunoglobulin of claim 36, where the K_a affinity is at least about 10^9 M^{-1}.

40. (added in amendment 6/11/99) An isolated human sequence immunoglobulin that specifically binds human CD4 or an antigenic fragment thereof comprising a human sequence immunoglobulin heavy chain polypeptide having a VDJ junction comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, and SEQ ID NO:9.

41. (added in amendment 6/11/99) An isolated or transformed cell comprising a human sequence immunoglobulin which binds to an antigen with a K_a affinity of at least about 10^8 M^{-1}.

42. (added in amendment 6/11/99) The cell of claim 41, wherein the K_a affinity is at least about 10^9 M^{-1}.

43. (added in amendment 6/11/99) The cell of claim 41, wherein the antigen is a human antigen.

44. (added in amendment 6/11/99) The cell of claim 41, wherein the antigen is CD4 or an antigenic fragment thereof.

45. (added in amendment 6/11/99) The cell of claim 41, wherein the cell is a mouse cell.

46. (added in amendment 6/11/99) The transformed cell of claim 10, wherein the human sequence immunoglobulin polypeptide has the same sequence as an immunoglobulin polypeptide secreted by a hybridoma obtained from a transgenic mouse.

47. (added in amendment 6/11/99) The transformed cell of claim 46, wherein said transgenic mouse comprises a homozygous pair of functionally disrupted endogenous heavy chain alleles or a homozygous pair of functionally disrupted endogenous light chain alleles or a homozygous pair of functionally disrupted endogenous heavy and light chain alleles, and a human immunoglobulin light chain transgene, or a human heavy chain transgene, or a human immunoglobulin light chain transgene and heavy chain transgene.

48. (added in amendment 6/11/99) The transformed cell of claim 11, wherein the eukaryotic cell is a SP20 cell line or an NSO cell line.

49. (added in amendment 6/11/99) The transformed cell of claim 11, wherein the eukaryotic cell is a CHO cell or a myeloma-derived cell.

50. (added in amendment 6/11/99) The human sequence immunoglobulin of claim 13, wherein the human sequence light chain variable region comprises an amino acid sequence encoded by SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, or SEQ ID NO:10.

51. (added in amendment 6/11/99) The human sequence immunoglobulin of claim 13, wherein the human sequence heavy chain variable region comprises an amino acid sequence encoded by SEQ ID NO:1, .SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, or SEQ ID NO:9.

52. (NEW) The transformed cell of claim 10, wherein the cell is a eukaryotic cell.

53. (NEW) A hybridoma secreting a human sequence immunoglobulin, wherein the immunoglobulin is selected from the group consisting of:

a human sequence immunoglobulin comprising a VH4-34 segment, a DXP'1 segment, a JH4 segment, and a heavy chain CDR3 region comprising the sequence DITMVRGPH (SEQ ID NO:63),

a human sequence immunoglobulin comprising a VH5-51 segment, a DHQ52 segment, a JH2 segment, and a heavy chain CDR3 region comprising the sequence PANWNWYFVL (SEQ ID NO:64),

a human sequence immunoglobulin comprising a VH4-34 segment, a JH5 segment, and a heavy chain CDR3 region comprising the sequence VINWFDP (SEQ ID NO:65),

a human sequence immunoglobulin comprising a VH5-51 segment, a DHQ52 segment, a JH4 segment , and a heavy chain CDR3 region comprising the sequence DQLGLFDY (SEQ ID NO:66),

a human sequence immunoglobulin comprising a VkA27/A11 segment, a Jk4 segment, and a light chain CDR3 region comprising the sequence QQYGSSPLT (SEQ ID NO:67),

a human sequence immunoglobulin comprising a VkL18 segment, a Jk4 segment, and a light chain CDR3 region comprising the sequence QQFISYPQLT (SEQ ID NO:68),

a human sequence immunoglobulin comprising a VkL19 segment, a Jk2 segment, and a light chain CDR3 region comprising the sequence QQANSFPYT (SEQ ID NO:69), and

a human sequence immunoglobulin comprising a VkL15 segment, a Jk2 segment, and a light chain CDR3 region comprising the sequence QQYDSYPYT (SEQ ID NO:70).